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The Pharmacy Drug Company

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January 28, 2002

Food and Drug Administration
Dockets Management Branch
5630 Fishers Lane
Room 1061 – HFA-305
Rockville, MD 20852

Re: Docket No. 01D-0488 Guidance for Industry
Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling, October, 2001

On behalf of the Eon Laboratories, Inc. I would like to comment on the Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling, October, 2001, Docket No. 01D-0488. We appreciate the effort that the Agency has made in preparing this guidance. We hope that the following comments will be useful to the Agency.

Lines 67-68

Food effects on BA are generally greatest when the drug product is administered immediately after a meal is ingested.

Comments

We are not sure whether taking a drug product immediately after a meal is ingested or in the middle of a meal results in less "food effect" on BA. For consistency in study design, we recommend the following:.

Food effects on BA of the drug product should be determined shortly after a meal is ingested.

Lines 236-237

The meal should be consumed over 30 minutes with administration of the drug product immediately after the meal.

01D-0488 C8

Comments

Since study subjects eat at different rates, some of the subjects will finish their meal earlier than 30 minutes. This small variability in time for food consumption should not impact on the study. To coordinate meal consumption and administration of the drug product, we propose:

The meal should be started 30 minutes prior to the administration of the drug product. Study subjects must eat their meal within 30 minutes, Drug will be administered 30 minutes after the start of the meal.

Lines 259-268

The following exposure measures for assessment of BA and BE should be obtained from the resulting concentration-time curves for the test and reference products in food-effect BA and fed BE studies:

- *Total exposure, or area under the concentration-time curve (AUC0-inf, AUC0-t)*
- *Peak exposure (Cmax)*
- *Time to peak exposure (Tmax)*
- *Lag-time (tlag) for modified-release products, if present*
- *Terminal elimination half-life*
- *Other relevant pharmacokinetic parameters*

Comment:

All of these measures are not relevant to define BA or BE. Some of the measures are not robustly obtainable using the same pharmacokinetic methodology. For example, the lag-time (Tlag) parameter can only be robustly assessed using compartmental PK approaches.

The purpose of a BE study is to compare two formulations in terms of rate and extent of bioavailability. In pharmacokinetics, these processes are described by the parameters Ka (absorption rate constant) and F (bioavailability). Individual pharmacokinetic analysis using compartmental methods is very susceptible to noise in a data set. Estimation of the parameters, AUC (metric for extent of bioavailability) and Cmax (metric for rate of bioavailability) by noncompartmental analysis is robust and simple in most cases. We recommend that the PK parameters should only include those that can be robustly calculated by noncompartmental methods:

- Cmax
- Tmax
- AUC0-t
- AUC0-inf
- Kel

The parameters to pass bioequivalence should be limited to Cmax (indicative of rate and extent of bioavailability) and AUC0-inf (indicative of extent of bioavailability) using the noncompartmental approach.

Lines 315-317

For an ANDA, BE of a test product to the RLD product under fed conditions is concluded when the 90% CI for the ratio of population geometric means between the test and RLD product, based on log-transformed data, is contained in the BE limits of 80-125% for AUC and Cmax.

Comments

We feel that the requirement for 90% CI to be within the limits of 80-125% for AUC and Cmax is too restrictive and will make passing BE more difficult especially for highly variable drugs. The CI limits could be expanded, especially for Cmax to prevent the need for excessive subjects and to limit the exposure to the drug product. The requirement for 90% CI to be within the limits of 80-125% for AUC and Cmax should only be used if the fed study is the pivotal BE study.

Comments on AUC 0-t and AUCinf

Passing on both the AUC0-t and AUCinf should not be a strict criteria in a bioequivalence study. AUC0-t will be reflective of the AUCinf and an appropriate criteria for BE in the following circumstances:

- The PK has been correctly assessed (the observed AUC0-T should be on average 90% or more of the AUCinf)
- All collected samples are above the lower limit of quantification of the analytical method. If the latter is not true, then asking to pass on AUC0-t can be flawed scientifically. For example, one can end up comparing AUC0-36 with AUC0-24 within subjects in a crossover study.
- For some cases, the extrapolation of the terminal elimination half-life that is needed to estimate AUCinf is unobtainable in some of the study subjects. This may be the case for transdermal and extended release drug products.

Therefore, the extent of absorption should be reviewed with careful consideration the estimation for AUC0-t and AUC inf . The extent of BA should also be assessed by demonstrating that the extrapolated AUC is less than 10% on average (i.e., the AUC0-t/AUCinf ratio should be greater than 90%).

Lines 317-318

Although no criterion applies to Tmax, the Tmax values for the test and reference products are expected to comparable based on clinical relevance.

Comments

The term, "comparable" is vague and tends to be subjective. We feel that the Tmax should be provided for information purposes only.

We appreciate your consideration of our comments. Please contact us, if you have any questions or need clarification of our comments.

Yours truly,

Leon Shargel

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TO

FDA - Dockets Mgmt Branch

5630 Fishers Lane - Room 1061

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Dockets Mgmt 301 827 6860

Payment

Bill to:

Receiver ☐ 3rd Party ☐

☐ Paid in Advance

Origin Airbill Number

LI2 8598845566

AIRBORNE EXPRESS

1-800-247-2676

EXP (Letter - 150 lbs) X

NAS (Letter - 5 lbs)

SDS (Letter - 150 lbs)

Billing Reference (will appear on invoice)

# of Pkgs	Weight (LBS)	Packaging (One box must be checked)		
		Letter Express ☒	Express Pack ☐	Other Packaging ☐
1				

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☐ LAB ☐

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001 (07/00) S-08
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